Sinecatechins, a Defined Green Tea Extract, in the Treatment of External Anogenital Warts

A Randomized Controlled Trial

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OBJECTIVE: To estimate the clinical efficacy of topical sinecatechins, a defined green tea extract, in the treatment of external genital and perianal warts.

METHODS: This was a randomized, double-blind, vehicle-controlled trial involving 502 male and female patients aged 18 years and older, with 2–30 anogenital warts ranging from 12 to 600 mm^2 total wart area. Patients applied sinecatechins ointment 15% or 10% or vehicle (placebo) three times daily for a maximum of 16 weeks or until complete clearance of all warts, followed by a 12-week treatment-free follow-up to assess recurrence.

RESULTS: Complete clearance of all baseline and newly occurring warts was obtained in 57.2% and 56.3% of patients treated with sinecatechins ointment 15% and 10%, respectively, compared with 33.7% for vehicle (both $P<.001$). Significance was observed at weeks 4 and 6 and all subsequent visits. Numbers needed to treat were 4.3 and 4.4. Partial clearance rates of at least 50% were reported for 78.4% and 74.0% of patients in the sinecatechins ointment 15% and 10% groups compared with 51.5% of vehicle patients. During follow-up, recurrence of any wart was observed in 6.5%, 8.3%, and 8.8% in the sinecatechins ointment 15% group, sinecatechins ointment 10% group, and vehicle patients, respectively. A total of 3.7%, 8.3%, and 0.0% developed new warts, respectively. A total of 87.7% and 87.3% of patients in the sinecatechins ointment 15% and 10% groups, and 72.1% of vehicle patients experienced application site reactions; 49.2%, 46.2%, and 65.4% of those, respectively, were mild or moderate.

CONCLUSION: Topical sinecatechins ointments 15% and 10% are effective and well-tolerated in the treatment of anogenital warts.

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LEVEL OF EVIDENCE: I

Visible external anogenital warts (condylomata acuminata) are nonmalignant squamous cell tumors caused by infections of the human papillomavirus (HPV). External anogenital warts are one of the fastest growing sexually transmitted diseases, affecting approximately 1% of sexually active adults in the United States and Europe, with a further 15% having subclinical infections. Worldwide, approximately 30 million cases of genital warts are diagnosed annually. In both the United States and Europe, more than 1 million new cases of external anogenital warts are diagnosed every year.[1–3]

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For a list of the investigators and hospitals who participated in this study, see the Appendix online at www.greenjournal.org/cgi/content/full/111/6/1371/DC1.

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Dr. Tatti has served as a clinical study investigator (contracted research) for MediGene AG (Munich, Germany). Dr. Swinehart was one of the study investigators, and for this purpose he has a contract with MediGene AG. Dr. Thielert, Professor Tawfik, and Dr. Mescheder are employees of MediGene AG, and they receive a salary from and own stock in the company. Dr. Beutner is a study investigator, consultant, congress speaker, and holds membership on the advisory committee for MediGene AG. He is a consultant and shareholder in Epitome Pharmaceuticals (Halifax, Nova Scotia).

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Although the condition is not life threatening, it can cause substantial discomfort, pain, and problems with sexual intercourse. Therapies for external anogenital warts include patient-administered topical treatments, such as imiquimod (5% cream)[4] and podophyllotoxin (0.15% cream or 0.5% solution),[5] and physician-administered therapies, such as cryotherapy, curettage and electrodesiccation, laser surgery, podophyllin resin, and trichloroacetic acid treatment.[6] These therapies are associated with painful side effects, mainly erythema, ulcerations, and possible tissue destruction and scarring.[6,7] A common problem is wart recurrence. Recently, prophylactic HPV vaccines have been shown to prevent acquisition of HPV and the development of external anogenital warts[8] but are not considered as a therapeutic approach. Therefore, there is a need for new and improved treatments for external anogenital warts.

Sinecatechins are a standardized extract of green tea leaves from *Camellia sinensis,* a species of the *theaceae* family, containing mainly tea polyphenols, particularly catechins (more than 85%). The main catechin in sinecatechins ointment is (-)-epigallocatechin gallate, which has the highest biologic activity. Green tea catechins exert multiple biologic activities, involving potent antiviral and antioxidant activity. Catechins bind to a number of proteins, including enzymes involved in the generation of inflammatory mediators, proteases promoting tumor invasion, and kinases needed in tumor cell signaling, cell cycle modification, and induction of apoptosis.[9–12] These postulated immune-stimulatory, antioxidative, antiviral, and antitumor properties presumably contribute to the therapeutic effect of sinecatechins ointment[13,14] (MediGene AG, unpublished data).

In the last years, two phase III randomized, double-blind, vehicle-controlled trials were conducted in Europe, South Africa, and the Americas to evaluate safety and the efficacy of sinecatechins ointments 15% and 10% compared with vehicle for complete clearance of all (baseline and new) external anogenital warts. In the present work, we are estimating the clinical efficacy and present the safety results of the Americas phase III study.

MATERIALS AND METHODS

The study was a multicenter, randomized, double-blind, vehicle-controlled, three-arm parallel-group phase III trial, conducted in 50 health centers in the United States, Latin America, and Romania, between July 2003 and August 2004. The relevant authority and responsible local and/or national independent ethics committees or institutional review boards approved the study protocol and any other relevant study documentation before patient enrollment. Written informed consent was obtained from each patient after providing detailed information about the study. The trial was performed according to the Declaration of Helsinki, Somerset West, 1996[15] and the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guideline as well as to the demands of national drug and data protection laws and other applicable regulatory requirements, and was fully monitored and audited. This article was produced according to the Good Publication Practice Guidelines for Pharmaceutical Companies.[16]

Male and female outpatients, aged 18 years or older, clinically diagnosed with 2 to 30 external genital and perianal warts with a total wart area of 12 mm^2 to 600 mm^2 were enrolled at dermatology, gynecology, and urology services of participating hospitals and practices. Female patients with child bearing potential had to have negative pregnancy test at the time of enrollment. Also, male patients and female partners of male patients with child bearing potential had to use effective contraception during the treatment period.

Patients were excluded from the study if they presented with one of the following conditions: breast-feeding women; patients suffering from *Herpes genitalis*, acute or chronic infection with hepatitis B or C virus, human immunodeficiency virus, any other current or recurrent genital or uncontrolled infection, skin conditions that might interfere with the study drug, or internal (vaginal or rectal) warts that required treatment; organ allograft recipients; former or current participants of an investigational trial; patients who had treatment for external anogenital warts or had systemic intake of virostatics (with the exception of systemic acyclovir and analogues) or immunosuppressive medication within 30 days before enrollment.

Patients were randomly assigned to receive sinecatechins ointment 15%, sinecatechins ointment 10%, or vehicle in a 2:2:1 allocation ratio according to a randomization list generated by a random number generator using the method of permuted blocks (block size=5). The maximum duration of treatment was 16 weeks or until complete clearance of all (baseline and new) warts, whichever came first, followed by a 12-week treatment-free follow-up phase for complete responders to assess wart recurrence. Participating centers were provided with blinded medication kits that had a preassigned patient number, with each patient allocated to the lowest available number. The randomization list was never available to investigators or the project team. Vehicle was of identical color and consistency as sinecatechins ointments to ensure blinding.

During the screening visit before the first study visit (baseline visit), inclusion and exclusion criteria, disease and medical history, demographic data, local skin reactions, vital signs, and previous and concomitant medications of potentially eligible patients were recorded. Laboratory evaluation, including a pregnancy test (females only), hematology, blood chemistry and urinalysis, and a physical examination were also performed. At the baseline visit, the inclusion and exclusion criteria, local skin reactions, adverse events, physical examination results, vital signs, and previous and concomitant medications were reviewed, eligible patients were randomly allocated to one of the three treatment groups, and the trial medication was dispensed. The 15%, 10%, or vehicle ointments were presented in 15-g aluminum tubes (one tube for 2 weeks of treatment) prepared by Haupt Pharma, Berlin, Germany. Trial staff supervised the initial application. Trial patients were instructed to apply the medication to all external anogenital warts three times per day, 8 hours apart, until all warts completely healed or for a maximum of 16 weeks of treatment, whichever occurred first. Data on treatment adherence was collected at each visit through the weighing of drug tubes. During the 16-week treatment period, control visits were scheduled every 2 weeks. Wart measurements, local tolerability, adverse events, and concomitant medications were recorded at each control visit. Oral paracetamol or acetaminophen were prescribed for local skin reactions that required treatment. Other topical treatments were not allowed. Female patients as well as partners of male patients were prescribed contraception during the treatment period.

Patients with complete clearance of all warts stopped treatment and entered into the follow-up period. Laboratory evaluations, including a pregnancy test (females only), a physical examination, and vital signs measurement were carried out again at the end of treatment. Photo documentation was requested for at least the baseline and end of treatment visits.

Follow-up visits were scheduled 4 and 12 weeks after the end of treatment to obtain data on recurrent and new external anogenital warts. At both visits, local tolerability was evaluated and previously reported adverse events and concomitant medications were updated.

Wart clearance was determined as the percentage reduction of the wart area (ie, maximal wart length perpendicular to maximal wart width) at the final evaluation relative to the area when the wart was first detected. Locations of baseline and new warts as well as recurrent warts were recorded and distinguishably labeled on a dermagram. Photographs served to document wart clearance or progression.

Safety assessments included the occurrence of any adverse effects. Local skin reactions at the application site represent a special safety issue for topically applied treatments. Therefore, they were evaluated and described separately from other adverse events. Solicited objective local skin signs (erythema, edema, induration, vesicles, erosion/ulceration, or other, and overall evaluation of skin reaction) were assessed by the investigator as none, mild, moderate, or severe. Patients were asked to grade the worst intensity of experienced solicited local skin symptoms (burning, itching, pain, other, and overall evaluation of skin symptoms) as none, mild, moderate, or severe. Adverse events other than local reactions at the application site reported by the patient were assessed according to the same grading.

Patient's adherence to the treatment schedule was rated by the investigator on a three-point scale (more than 90%, 65% to 90%, less than 65% compliance) based on the patient's adherence to the treatment application frequency per day (three times daily) and per visit interval (daily for 2 weeks) and control of the weight of the dispensed medication tubes.

Sample size calculations were based on data from a previous phase II–III study with12-week treatment duration.[17] We hypothesized that rates for complete clearance of all warts were 65% and 55% for the sinecatechins ointments 15% and 10%, respectively, and 35% for vehicle. A total of 400 patients (160 patients for both active treatment groups and 80 patients for the vehicle group, assuming a 2:1 randomization ratio) were required to detect a 20% significant difference at a 5% alpha level (two-tailed) with a power of 80%. To compensate for nonevaluable patients, 480 patients were needed in total.

Efficacy analyses were performed on data from the intent-to-treat population, including all patients enrolled with the baseline and at least one postbaseline observation of the wart area. The primary efficacy endpoint was analyzed by comparing the proportion of patients with complete clearance of all warts in each active treatment group to vehicle, following the Hochberg multiple testing procedure with an alpha level of 5%.[18] Secondary efficacy analyses were performed on both the intent-to-treat and the per-protocol (all patients without any major protocol deviations) populations. For categorical data, differences among the different treatment groups with respect to demographic and clinical variables as well as for primary and secondary endpoints were analyzed by means of Fisher exact test. For quantitative

numerical data an analysis of variance was performed. Odds ratios and related 95% confidence intervals (CIs) were estimated for both active-to-vehicle comparisons. All statistical tests applied were two-tailed. Two-tailed tests were performed at a 5% level of significance (α=.05).

The safety analysis population included all randomly assigned patients treated at least once with study medication. All safety analyses were performed on this safety population, stratified by gender. Statistical analysis was performed using SAS 8.02 software (SAS Institute Inc., Cary, NC).

RESULTS

A total of 502 eligible patients (258 males and 244 females) were randomly assigned to apply sinecatechins 15% (196 patients), 10% (202 patients), or vehicle ointment (104 patients) (Fig. 1). Seven patients were excluded from the analysis due to lack of any postbaseline data. The intention-to-treat analysis is therefore based on 495 patients (254 male and 241 female patients).

The treatment groups were comparable with respect to baseline characteristics (Table 1). Genitourinary system findings were reported in 55 (28.1%), 55 (27.2%), and 38 (36.5%) patients in the sinecatechins ointment 15%, 10%, and vehicle groups, respectively.

Most patients (414 [82.5%]) did not have previous episodes of external anogenital warts; 59 (11.8%) patients previously had one episode, 20 (4.0%) patients had two episodes, and nine (1.8%) patients had three or more episodes. The mean time between the start of the current episode and start of treatment was 44, 55, and 48 weeks in the sinecatechins ointment 15%, 10%, and vehicle groups, respectively.

Baseline warts were mainly located on the vulva (207 [41.2%] female patients) and the penis shaft (185 [36.9%] male patients), followed by the perianal area (91 [18.1%] patients), perineal area (77 [15.3%] patients), and glans penis (59 [11.8%] male patients).

Table 2 shows the proportion of patients with complete clearance of all (baseline and new) external anogenital warts. One hundred eleven (57.2%) pa-

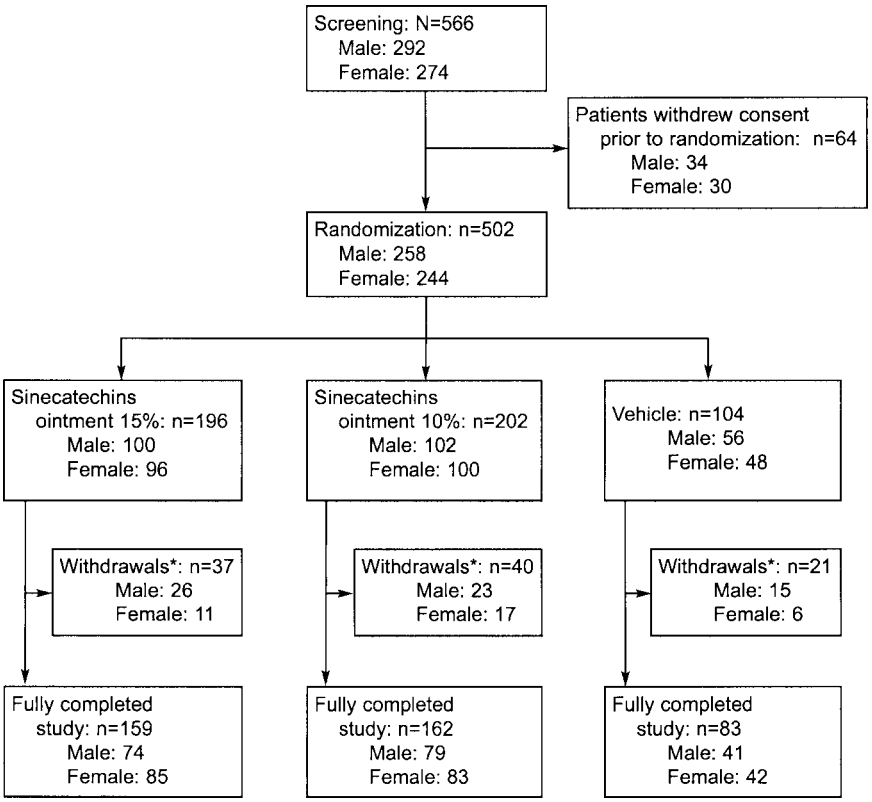

Fig. 1. Disposition of study patients. This is a flow diagram of patient progress through the phases of this randomized, vehicle-controlled study. Patients were randomly assigned to one of the three treatment groups in a 2:2:1 ratio to sinecatechins ointment 15%, sinecatechins ointment 10%, or vehicle. *In this group of withdrawals, there were also those seven patients (two patients receiving sinecatechins ointment 15% and five patients receiving sinecatechins ointment 10%) who withdrew consent after randomization/baseline visit and thus did not have any postbaseline assessment. They were therefore not included in the efficacy analyses. The most frequently cited primary reasons for premature discontinuation were "patient withdrew consent" in 14 (7.1%), 15 (7.4%), and 4 (3.8%) patients in the sinecatechins ointment 15%, 10%, and vehicle groups, respectively, and "lack of efficacy/treatment failure" in seven (3.6%), four (2.0%), and six (5.8%) patients, respectively. An adverse event was documented as the primary reason for premature termination by only 1 (0.2%) patient (severe vulvitis; in the sinecatechins ointment 15% group).

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Table 1. Baseline Characteristics

	Sinecatechins Ointment 15%	Sinecatechins Ointment 10%	Vehicle	*P*
Study population	196 (100.0)	202 (100.0)	104 (100.0)	
Gender				.857*
Male	100 (51.0)	102 (50.5)	56 (53.8)	
Female	96 (49.0)	100 (49.5)	48 (46.2)	
Ethnic group				.662*
White	57 (29.1)	67 (33.2)	29 (27.9)	
African	5 (2.6)	3 (1.5)	2 (1.9)	
Hispanic	134 (68.4)	131(64.9)	72 (69.2)	
Asian	0 (0.0)	1 (0.5)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	1 (1.0)	
Age (y)				.630†
Younger than 18	0 (0.0)	0 (0.0)	0 (0.0)	
18 to 30	120 (61.2)	125 (61.9)	62 (59.6)	
31 to 45	49 (25.0)	53 (26.2)	24 (23.1)	
46 to 65	23 (11.7)	22 (10.9)	14 (13.5)	
Older than 65	4 (2.0)	2 (1.0)	4 (3.8)	
Mean age ± SD (y)	31.2±12.26	31.3±11.53	32.5±12.95	
Median age (range) (y)	27.0 (18–90)	28.0 (18–83)	28.0 (18–73)	
Smoking history				.878*
Nonsmoker	101 (51.5)	97 (48.0)	54 (51.9)	
Previous	19 (9.7)	17 (8.4)	8 (7.7)	
Current	76 (38.8)	88 (43.6)	42 (40.4)	
Childbearing potential (female patients only)				.892*
Yes	76 (79.2)	80 (80.0)	40 (83.3)	
No	20 (20.8)	20 (20.0)	8 (16.7)	
Circumcision (male patients only)				.386*
Yes	24 (24.0)	17 (16.7)	13 (23.2)	
No	76 (76.0)	85 (83.3)	43 (76.8)	

SD, standard deviation.
Data are n (%) unless otherwise specified.
* Fisher exact test.
† Analysis of variance model including study treatment as main effect.

tients in the sinecatechins ointment 15% group, 111 (56.3%) patients in the sinecatechins ointment 10% group, and 35 (33.7%) patients in the vehicle group achieved complete clearance of all external anogenital warts ($P<.001$; Fisher exact test). This corresponds to numbers needed to treat of 4.3 and 4.4. The Breslow Day test for homogeneity of the odds rations across centers was not statistically significant for both active treatment groups. Superiority of both sinecatechins ointment 15% and 10% groups compared with vehicle was first observed at week 4 and week 6, respectively, and then at all subsequent visits.

Compared with males, the proportion of female patients with complete clearance of all warts was higher in all three treatment groups (Table 2). As for all patients, both genders in both the sinecatechins ointment 15% (women 64.6%; $P=.048$; men 50.0%; $P=.001$) and the sinecatechins ointment 10% (women 64.9%; $P=.003$; men 48.0%; $P=.003$) groups showed statistically significantly higher complete clearance rates of all warts when compared with vehicle (women 45.8%; men 23.2%).

Complete clearance of baseline warts was significantly higher for patients in the sinecatechins ointment 15% (58.8%) and 10% (60.9%) groups than for patients in the vehicle group (33.7%) (both $P<.001$). Analyses on the per-protocol population were very similar to those on the intent-to-treat population.

The proportion of patients with partial clearance of all warts greater than 50% was higher for the sinecatechins ointment 15% and 10% groups when compared with vehicle (Table 3). Clearance rates of at least 50% were reported for 152 (78.4%) patients and 145 (74.0%) patients in the sinecatechins ointment 15% and 10% groups compared with 53 (51.5%) of the vehicle patients (both $P<.001$; Wilcoxon rank sum test).

The median total wart number and median total wart area went to zero by the end of treatment in both sinecatechins ointment 15% and 10% groups but not in the vehicle group (Fig. 2). The median baseline differences were statistically significant (sinecatechins ointment 15% compared with placebo $P<.001$, sinecatechins ointment 15% compared with placebo $P<.014$).

Table 2. Complete Clearance of All Warts (Baseline and New) and Complete Clearance of Baseline Warts, All Patients and Stratified by Gender

	Sinecatechins Ointment 15% (n=194)	*P**	Sinecatechins Ointment 10% (n=197)	*P**	Vehicle (n=104)
Complete clearance of all warts					
All patients	111 (57.2)	<.001	111 (56.3)	<.001	35 (33.7)
Difference to vehicle	(23.5)		(22.6)		
OR (95% CI)	2.64 (1.61–4.33)		2.55 (1.55–4.17)		
NNT	4.3		4.4		
Males	49 (50.0)		48 (48.0)		13 (23.2)
Females	62 (64.6)		63 (64.9)		22 (45.8)
Complete clearance of baseline warts					
All patients	114 (58.8)	<.001	120 (60.9)	<.001	35 (33.7)
OR (95% CI)	2.81 (1.71–4.62)		3.07 (1.87–5.05)		
Males	51 (52.0)		52 (52.0)		13 (23.2)
Females	63 (65.6)		68 (70.1)		22 (45.8)

OR, odds ratio; CI, confidence interval; NNT, number needed to treat.
Data are n (%) unless otherwise specified.
* Two-tailed Fisher exact test.

Recurrence of any warts within the first 4 weeks of follow-up occurred in seven (6.5%) patients in the sinecatechins ointment 15% group, in seven (6.7%) patients in the sinecatechins ointment 10% group, and in three (8.8%) patients in the vehicle group. No additional recurrent warts were reported during the subsequent 8 weeks of follow-up in either the sinecatechins ointment 15% group or the vehicle group, whereas in the sinecatechins ointment 10% group, four (4.0%) patients suffered from recurrent warts. Thus, during the 12-week follow-up period, 6.5% and 8.3% of patients treated with sinecatechins ointment 15% and 10%, respectively, had recurrent warts compared with 8.8% of vehicle-treated patients. New warts appeared in four (3.7%) and nine (8.3%) patients in the sinecatechins ointment 15% and 10% group, respectively, and in none of the vehicle-treated patients throughout the follow-up.

At the baseline visit, 192 (38.2%) patients presented with local skin reactions; this percentage was similar in all three treatment groups. During treatment, 171 of 196 (87.7%) and 172 of 202 (87.3%) patients in the sinecatechins ointment 15% and 10% groups, respectively, and 75 of 104 (72.1%) of the vehicle patients experienced local application site reactions. Of those, 49.2%, 46.2%, and 65.4%, respectively, were mild or moderate. Number needed to harm calculated from these incidences were 6.4 (95% CI 3.9–17.2) and 6.6 (95% CI 4.0–18.5). The majority of local reactions were of mild to moderate intensity with less severe reactions. The predominant severe local skin reaction was itching in all three treatment groups: itching was diagnosed in 28 (14.7%) patients in the sinecatechins ointment 15% group, in 30 (16.1%) patients in the 10% group, and in two (3.2%) patients in the vehicle group. Local application site reactions increased by weeks 2 to 4 in all three treatment groups and gradually decreased thereafter during continued treatment.

Adverse events other than local reactions that were considered at least possibly related to study drug involved only 15 patients each on sinecatechins ointment 15% (7.7%) and 10% (7.4%). Most of the reported adverse events were of mild or moderate

Table 3. Levels of Clearance of All External Genital and Perianal Warts

Clearance Level	Sinecatechins Ointment 15% (n=194)	Sinecatechins Ointment 10% (n=196)	Vehicle (n=103)
Complete clearance 100%	111 (57.2)	111 (56.6)	35 (34.0)
Partial clearance 50% or more to less than 100%	41 (21.1)	34 (17.3)	18 (17.5)
Partial clearance 0 to less than 50%	32 (16.5)	32 (16.3)	31 (30.1)
Increase (less than 0%)	10 (5.2)	19 (9.7)	19 (18.4)

Data are n (%).

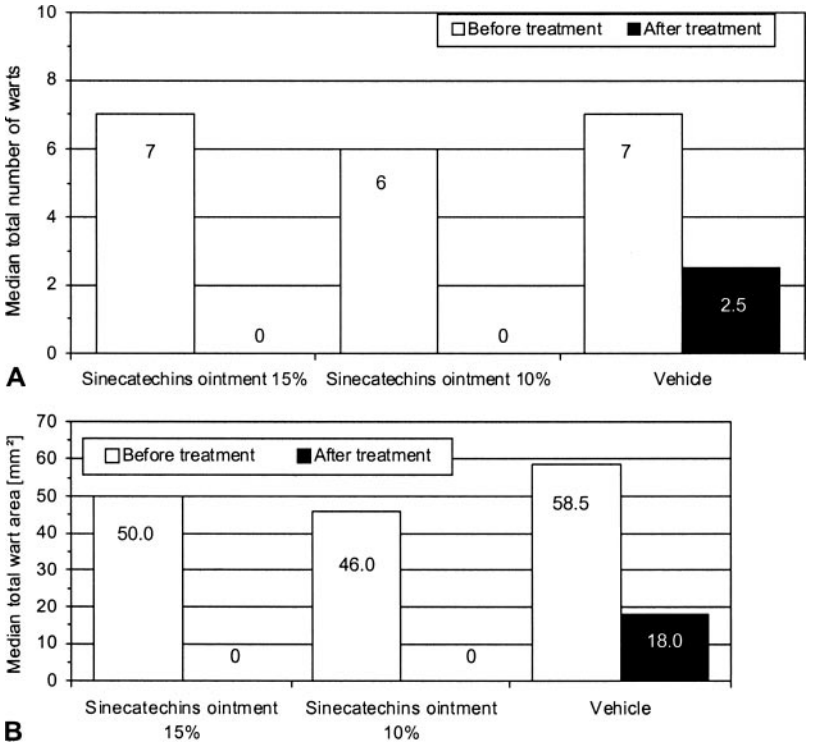

Fig. 2. Median total number of warts in the intent-to-treat population **(A)** and median total wart area in the intent-to-treat population **(B)** in the three treatment groups before (baseline visit; *white*) and after 16 weeks of treatment (visit 9; *black*). For both median total number of warts and median total wart area, reduction in the sinecatechins ointment 15% and 10% groups was 100% whereas in the vehicle group, reduction was 64% and 69%, respectively.

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intensity. The most frequently reported types of adverse events related to study medication were infections and infestations in 15 (3.0%) patients and blood and lymphatic system disorders in 10 (2.0%) patients. All other types of adverse events affected less than 2% of patients.

Severe related adverse events were documented for 5 (2.6%) and 2 (1.0%) patients treated with sinecatechins ointment 15% and 10%, respectively, including lymphadenitis, skin ulcer, vulvitis, and vulvovaginitis. Vulvitis was the only case of primary reason for discontinuation due to an adverse event (except for pregnancies).

Two (0.4%) patients presented with related serious adverse events; one patient had moderate application-site reactions, and one patient had severe vulvovaginitis in the sinecatechins ointment 15% and 10% groups, respectively. Both events resolved after treatment interruption and did not recur after reintroduction. No deaths occurred during the course of the study.

Treatment groups had comparable laboratory measurements, which were largely within the reference range. No clinically relevant abnormality was noted.

On average, 81.6%, 84.1%, and 95.2% of patients treated with sinecatechins ointment 15%, 10%, and vehicle, respectively, adhered well (more than 90% compliance) to the study drug application schedule at any given visit. Adequate adherence (compliance more than 65%) to the study drug application schedule was obtained in 96.7%, 96.6%, and 99.1% of patients treated in the sinecatechins ointment 15%, 10%, and vehicle groups, respectively.

DISCUSSION

External anogenital warts are one of the most frequent sexually transmitted diseases, and can cause pain, bleeding, difficulty with sexual intercourse, and social discomfort. However, there is no consensus in the medical community about which is the best available treatment. Sinecatechins ointment is a new drug derived from a natural product, green tea. The product was approved in October 2006 for commercialization in the United States by the U.S. Food and Drug Administration.[19] This study is one of the two independent pivotal phase III studies carried out to establish the efficacy and safety of the drug. We demonstrated a significantly higher complete clearance rate of all warts, ie, baseline and newly occurring warts during the treatment period, in patients who received sinecatechins ointments 15% and 10% when compared with those who received vehicle ointment. In addition, patients in both sinecatechins ointment groups had significantly higher complete clearance rates of baseline warts and lower number of recurrent

warts during the 12-week treatment-free follow-up. Therapeutic success, based on clearance rates of all warts of at least 50%, was observed in almost 80% of patients in both sinecatechins ointment groups.

In the present study, the primary efficacy endpoint was defined as complete clearance of all external anogenital warts. Previous clinical studies focused on complete clearance of baseline warts only; therefore, it is difficult to compare our results with complete clearance rates reported in studies analyzing other treatment options. Complete clearance rates of baseline warts reported by clinical trials that evaluated the efficacy of 0.5% podofilox were in the 45–82% range.[20,21] Clearance rates of baseline warts reported for imiquimod 5% cream varied between 35% and 85%.[20,21] Treatment with sinecatechins ointment 15% achieved complete clearance of all (baseline and new) warts in 57.2% of patients and, even better, in 67.7% of all patients in a subgroup of patients who completed the 16-week treatment period with or without complete wart clearance. These findings demonstrate that sinecatechins ointment has a clinical efficacy comparable or superior to other marketed products such as imiquimod 5% cream and 0.5% podofilox.

The rate of complete clearance in patients treated with the vehicle was somewhat higher than the spontaneous healing rates of up to 40% reported for dermatological treatment.[20,22,23] Thorough care and increased hygiene during the treatment period combined with frequent mechanical interaction during the application of the vehicle ointment containing ingredients known as skin irritants may have contributed to skin healing.

It is worth noting that although clearance rates for sinecatechins ointment were higher in females than in males, the gender difference was relatively small. Lower clearance rates in males have been linked to greater keratinization of the skin affecting drug penetration,[24,25] particularly on the penile shaft, the most common location of warts in males. The auspicious complete clearance rates for both gender obtained with sinecatechins ointment indicate that its efficacy may be less affected by keratinization of the skin compared with other treatment options.

Rates of recurrence were low, with 6.5% and 8.3% of patients in the sinecatechins ointment 15% and 10% groups alike, and the rates of new warts, which appeared after the treatment period, were 3.7% and 8.3% of patients, respectively. Cryotherapy, one of the most widely used options, is associated with 20% to 40% recurrence rates. Likewise, recurrence rates of imiquimod 5% cream and podofilox range from 13% to 19% and up to 91%, respectively.[20,21] Our results suggest that topical application of sinecatechins ointment unmask and heal subclinical wart lesions, thereby contributing to the low rate of recurrent and new warts after end of treatment.

The vast majority of adverse effects of sinecatechins ointment were mild to moderate local application-site reactions, which reached an early maximum at weeks 2 to 4 and subsided during treatment. Preclinical findings indicate that sinecatechins ointment stimulates the immune system by release of proinflammatory cytokines (eg, interleukin-1, interferon γ, tumor necrosis factor α), which, in turn, elicit the observed local side effects like erythema, edema, itching, etc. (own unpublished data). This suggests that local reactions at the application site are indicative of and essential for achieving clinical response.

Overall, the number of patients with study treatment–related adverse events other than local reactions was remarkably low. The data confirm result of the prior identically designed pivotal study of sinecatechins ointments (15% and 10%).[26] This phase III trial carried out in Europe and South Africa yielded only 2% of patients who had adverse events related to sinecatechins ointment (article submitted).

The fact that data were collected from a variety of university, general hospitals, and clinical practices from different countries gives excellent validity to the trial. In addition, comparability among study groups was assured, because there were no significant differences with respect to demographic and baseline characteristics of patients with different treatment options.

In summary, our results indicate that sinecatechins ointment is an effective, well tolerated, self-applicable, topical treatment option to clear all baseline and new external anogenital warts and keep patients wart-free. Although HPV vaccination will certainly change prevention and management of the disease, topical treatment of external anogenital warts is, and still will be, an inevitable modality for visible as well as invisible (subclinical) lesions, because not all patients are eligible for vaccination, and available vaccine(s) are not therapeutic. Intraanal, (intra)vaginal, and cervical condylomas, as well as other intraepithelial lesions, may constitute a future area of medical attendance of this unique and promising herbal product.

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